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(54) Title: USE OF SYNERGISTIC COMBINATIONS OF A NK_1 RECEPTOR ANTAGONIST AND A GABA ANALOG IN PSYCHIATRIC DISORDERS

(57) Abstract: The present invention provides methods of treatment using synergistic combinations of a NK_1 receptor antagonist and a GABA analog, and pharmaceutical compositions and products containing the NK_1 receptor antagonist and GABA analog. The present invention provides the use of a NK_1 receptor antagonist and a GABA analog for the manufacture of a medicament for the treatment or prevention of psychiatric disorders.

USE OF SYNERGISTIC COMBINATIONS OF A NK_1 RECEPTOR ANTAGONIST AND A GABA ANALOG IN PSYCHIATRIC DISORDERS

FIELD OF THE INVENTION

This invention relates to a method for preventing and for treating psychiatric disorders through the use of effective amounts of synergistic NK_1 receptor antagonist/GABA analog combinations.

BACKGROUND OF THE INVENTION

Neurokinin 1 (NK_1) receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinins.

A selective NK_1 receptor antagonist, [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester, has been shown in the rat to block the maintenance of streptozocin-induced static allodynia (Field *et al.*, (1998) J. Pharmacol. Exp. Ther. **285**: 1226-1232).

Gabapentin (1-(aminomethyl)cyclohexane acetic acid) is an antiepileptic drug.

SUMMARY OF THE INVENTION

It has now been discovered that combination therapy with a NK_1 receptor antagonist and a GABA analog results in dramatic improvement in psychiatric disorders control. When administered together, the NK_1 receptor antagonist and the GABA analog can interact in a synergistic manner to control a psychiatric disorder. This unexpected synergy allows a reduction in the dose required of each

compound, leading to a reduction in the side effects, and enhancement of the clinical utility of the compounds.

Accordingly, this invention provides a method for preventing or treating a psychiatric disorder comprising administering to a subject in need of treatment an amount of a synergistic combination of a NK_1 receptor antagonist and a GABA analog.

Preferably, the psychiatric disorder treated is anxiety, panic attack, generalized anxiety disorder, social phobia or depression.

The invention also concerns the use of a composition comprising synergistic effective amounts of a NK_1 receptor antagonist and a GABA analog, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating a psychiatric disorder.

BRIEF DESCRIPTION OF THE DRAWING

FIGURE 1. Dose response 30 min post drug for [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (CI-1021) in the isolation-induced vocalization model of anxiety in the guinea pig pup. Results are shown as mean % reduction ± SEM in the number of calls *vs.* baseline measurements taken before the treatment.
*: $P<0.05$ *vs* vehicle group; #: $P<0.05$ *vs* their own vehicles (not included in the graph for clarity); Kruskall-Wallis test followed by Mann-Whitney test.

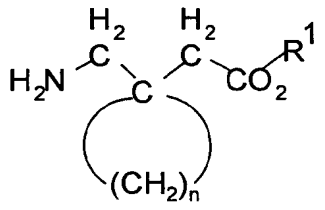
DETAILED DESCRIPTION OF THE INVENTION

According to this invention, a NK_1 receptor antagonist is used in combination with a GABA analog to treat a psychiatric disorder in patients in need of such

treatment. The compounds can be employed individually or can be combined in a single formulation, for example as a tablet, capsule, syrup, solution, as well as controlled release formulations. In a preferred embodiment, the NK_1 receptor antagonist and GABA analog are formulated individually and administered in the same manner that each is normally used clinically, but with reduced amounts of each.

The NK_1 receptor antagonists, such as capsaicin can be used herein. Specific NK_1 receptor antagonists that can be used herein are disclosed in U.S. Patent Nos. 3,862,114, 3,912,711, 4,472,305, 4,481,139, 4,680,283, 4,839,465, 5,102,667, 5,162,339, 5,164,372, 5,166,136, 5,232,929, 5,242,944, 5,300,648, 5,310,743, 5,338,845, 5,340,822, 5,378,803, 5,410,019, 5,411,971, 5,420,297, 5,422,354, 5,446,052, 5,451,586, 5,525,712, 5,527,811, 5,536,737, 5,541,195, 5,594,022, 5,561,113, 5,576,317, 5,604,247, 5,624,950, and 5,635,510; World Patent Application Nos. WO 90/05525, WO 91/09844, WO 91/12266, WO 92/06079, WO 92/12151, WO 92/15585, WO 92/20661, WO 92/20676, WO 92/21677, WO 92/22569, WO 93/00330, WO 93/00331, WO 93/01159, WO 93/01160, WO 93/01165, WO 93/01169, WO 93/01170, WO 93/06099, WO 93/10073, WO 93/14084, WO 93/19064, WO 93/21155, WO 94/04496, WO 94/08997, WO 94/29309, WO 95/11895, WO 95/14017; WO 97/19942, WO 97/24356; WO 97/38692, WO 98/02158, and WO 98/07694; European Patent Application Nos. 284942, 327009, 333174, 336230, 360390, 394989, 428434, 429366, 443132, 446706, 484719, 499313, 512901, 512902, 514273, 514275, 515240, 520555, 522808, 528495, 532456, and 591040. Preferred NK_1 receptor antagonists that can be used herein are disclosed in U.S. Patent No. 5,594,022; among these, a more preferred NK_1 receptor antagonist is [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester.

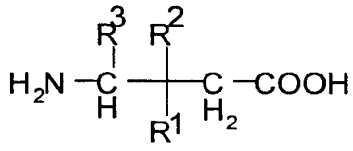
Any GABA structural analogs can be used within the context of the invention. Specific GABA analogs that can be used herein are disclosed in U.S. Patent Nos. 4,024,175 and 5,563,175, which are incorporated herein by reference. Preferred GABA analogs include a cyclic amino acid compound of Formula I:



(I)

wherein R^1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a GABA analog of Formula I where R^1 is hydrogen and n is 5, which compound is generically known as gabapentin. Other preferred GABA analogs have Formula I wherein the cyclic ring is substituted, for example with alkyl such as methyl or ethyl. Typical of such compounds include (1-aminomethyl-3-methylcyclohexyl) acetic acid, (1-aminomethyl-3-methylcyclopentyl) acetic acid and (1-aminomethyl-3-4-dimethylcyclopentyl) acetic acid.

In another embodiment, the method for preventing and treating a psychiatric disorder of the invention utilizes as a GABA analog a compound of Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein

R^1 is straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R^2 is hydrogen or methyl; and

R^3 is hydrogen, methyl, or carboxyl. Diastereoisomers and enantiomers of compounds of Formula II can be utilized in the invention. An especially preferred method of the invention employs as GABA analog a compound of Formula II where R^2 and R^3 are both hydrogen, and R^1 is $-(CH_2)_{0-2}$-iC_4H_9 as an (R), (S), or (R,S) isomer. A more preferred embodiment of the invention employs, as GABA analog, 3-aminomethyl-5-methyl-hexanoic acid, and especially (S)-3-amino-methyl-5-methyl-hexanoic acid, known generically as pregabalin. Another preferred compound of Formula II is 3-(1-aminoethyl)-5-methyl-heptanoic acid.

The dosage of each agent will vary depending upon the severity of the disease or disorder, the frequency of administration, the particular agents, and combinations utilized, and other factors routinely considered by an attending medical practitioner. The NK_1 receptor antagonist is normally administered at a daily dose of from about 0.25 mg to about 500 mg, typically about 3 mg to about 250 mg. The GABA analog is normally administered at doses from about 5 mg to about 2500 mg per day, and more typically from about 50 mg to about 1500 mg per day. A preferred GABA analog is gabapentin, and it is employed at doses from about 100 mg to about 1000 mg per day.

A NK_1 receptor antagonist utilized in the present invention includes solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the NK_1 receptor antagonist.

A GABA analog utilized in the present invention includes solvates, hydrates, pharmaceutically acceptable salts, and polymorphs (different crystalline lattice descriptors) of the GABA analog.

Where it is appropriate to form a salt of the NK_1 receptor antagonist or of the GABA analog, the pharmaceutically acceptable salts include acetate, benzene-sulfonate, benzoate, bitartrate, calcium acetate, camsylate, carbonate, citrate, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycoloylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydrogencarbonate, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate or hemi-succinate, sulfate or hemi-sulfate, tannate, tartrate or hemi-tartrate, theoclate, triethiodide, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine, procaine, aluminum, ammonium, tetramethyl ammonium, calcium, lithium, magnesium, potassium, sodium, and zinc. (See also "Pharmaceutical salts" by Berge S.M. *et al.* (1997) J. Pharm. Sci. **66**: 1-19, which is incorporated herein by reference.)

The terms "patient" and "subject" are intended to include a mammal, especially a human.

The term "psychiatric disorder" is intended to include anxiety, panic attacks, generalized anxiety disorder, social phobia and depression.

All that is required to practice the method of preventing and treating a psychiatric disorder according to the present invention is to administer a synergistic NK_1-GABA analog combination in an amount that is effective to prevent or treat the disorder, i.e. to control the psychiatric disorder.

In a further aspect of the present invention, there is provided a pharmaceutical composition for the treatment or prevention of a psychiatric disorder comprising the synergistic NK_1 antagonist - GABA analog combination. Formulating the active components of the combination in dosage unit form with at least one pharmaceutically acceptable carrier or excipient produces pharmaceutical formulations of the composition according to the present invention. For preparing pharmaceutical formulations from the compounds used in this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. They preferably contain 5% to about 70% of the active components of the combination. In such solid dosage forms, the active components are admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol, and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In

the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well known in the art. They can also be of such composition that they release the active components in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions that can be used are polymeric substances and waxes. The active components of the combination can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active components of the combination, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, and the like.

Suspensions, in addition to the active components, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the active components of the combination of the present invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature, and therefore melt in the rectum and release the active components of the combination.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions of the active components of the combination, and also sterile powders for reconstitution into sterile injectable solutions or dispersions.

Examples of suitable liquid carriers, diluents, solvents or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), and suitable mixtures thereof.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispersing agents. Various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like can ensure prevention of the action of microorganisms. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active components of the combination. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms. Some examples of dosage unit forms are tablets, capsules, pills, powders, suppositories, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses.

The percentage of the active components in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10 % in a solid composition and at least 2 % in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active components is present, for example, from 10 % to 90 % by weight.

Routes of administration of the active components of the combination or their respective salts are parenteral or, preferably, oral. For example, a useful oral dosage is between 20 and 800 mg , expressed as the mass of the GABA analog, and a useful intravenous dose is between 5 and 50 mg. The dosage is within the dosing range used in treatment of a psychiatric disorder, or as would be dictated by the needs of the patient as described by the physician.

The invention provides compositions of a NK_1 receptor antagonist and a GABA analog, and a method of treating a psychiatric disorder comprising administering to a patient in need of treatment an amount of a NK_1 receptor antagonist and an effective amount of a GABA analogue effective in this psychiatric disorder. Any NK_1 receptor antagonist can be combined with any GABA analog according to this invention. Preferred GABA analogs to be employed are the compounds of Formula I and II, especially gabapentin and pregabalin. Preferred NK_1 receptor antagonists to be employed in the compositions include (2-methoxy-benzyl)-((2S,3S)-2-phenyl-piperidin-3-yl)-amine, and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester.

When the GABA analog and the NK_1 receptor antagonist are formulated together, the composition contains about 1 to about 1000 parts by weight of GABA analog, and about 1000 to about 1 part by weight NK_1 receptor antagonist. Preferred ranges for the ratio of the two active principles, expressed as parts by weight of the GABA analog relative to parts of the NK_1 receptor antagonist, are 50:1 to 1:1. A most preferred range for the ratio of the two active principles is 20:1. For example a typical composition of gabapentin and [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester contains about 400 mg of gabapentin and about 20 mg of the NK_1 receptor antagonist. Such combination is administered to an adult patient about twice a day to achieve a synergistic control of a psychiatric disorder. The compositions may contain common pharmaceutical excipients such as those described above.

The advantages of using the combination of a NK_1 receptor antagonist and a GABA analog of the instant invention include the selective activity of the combination on a psychiatric disorder, the relatively nontoxic nature of the combination, the ease of preparation, the fact that the combination is well tolerated, and the ease of *i.v.* and, in particular, oral administration of the combination.

The ability of synergistic NK_1-receptor antagonist-GABA analog combinations to prevent or treat a psychiatric disorder has been established in several animal models.

EXAMPLE 1

Synergistic interaction between a NK_1-receptor antagonist and a GABA analog in isolation-induced vocalizations of guinea-pig pups

Methods:

Distress vocalizations of guinea-pig pups (2-14 days old) are quantified in a 5-min isolation period, after which they are reunited with their mothers and littermates. The test cage consists of a sound-attenuating box with a white interior and white illumination. The vocalizations are recorded by means of a microphone and a digital audio tape (DAT) recorder. Pups are first selected using the criterion of emitting a minimum of 500 vocalizations after three pre-tests on three consecutive days. On the day of the test, pups are submitted to a pre-treatment (baseline) measurement. Each pup then receives oral administration of test compounds and is returned to the home cage for 30 min before maternal separation.

Different ratios of combinations of doses are administered to groups of animals (n= 9-10 per group). A minimum of 3 total doses for each ratio of combination is examined. The difference in the number of calls emitted before and after treatment is counted using Spike2 software; percentage of reduction in the number of calls is analyzed using a Kruskall-Wallis test followed by Mann-Whitney test between vehicle and different treatments. For example, the oral administration of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester (0.01-10.0 mg/kg *p.o.*, in Gelucire™ vehicle 30 min before the test) dose-dependently blocked vocalizations with a MED of 1.0 mg/kg (Figure 6). With different ratios of combinations of doses of a NK_1 receptor antagonist and a GABA analog, a synergistic interaction is considered when a significant shift to the left from the additive line is achieved.

The following examples illustrate typical formulations provided by the invention.

EXAMPLE 2

Tablet Formulation

Ingredient	Amount (mg)
[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)]	5
Gabapentin	100
Lactose	95
Corn starch (for mix)	20
Corn starch (paste)	20
Magnesium stearate (1%)	10
Total	250

The benzofuranyl-methyl ester, gabapentin, lactose, and corn starch (for mix) are blended to uniformity. The corn starch (for paste) is suspended in 400 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried. The dry granules are lubricated with the 1 % magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of a psychiatric disorder.

EXAMPLE 3

Preparation for Oral Solution

Ingredient	Amount
[2-(1H-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)]	20 mg
Pregabalin	400 mg

Sorbitol solution (70% N.F.)	40 mL
Sodium benzoate	20 mg
Saccharin	5 mg
Red dye	10 mg
Cherry flavor	20 mg
Distilled water q.s.	100 mL

The sorbitol solution is added to 40 mL of distilled water, and pregabalin and the benzofuranylmethyl ester are dissolved therein. The saccharin, sodium benzoate, flavor, and dye are added and dissolved. The volume is adjusted to 100 mL with distilled water.

EXAMPLE 4

Parenteral Solution

In a solution of 700 mL of propylene glycol and 200 mL of water for injection is added 0.5 g of [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and 10 g of pregabalin. The pH is adjusted to 6.5, and the volume is made up to 1000 mL with water for injection. The formulation is sterilized, filled into 5.0 mL ampoules each containing 2.0 mL, and sealed under nitrogen.

CLAIMS

What is claimed is:

1. A method for preventing or for treating a psychiatric disorder comprising administering to a patient in need of treatment an effective amount of a synergistic combination of a NK_1 receptor antagonist and a GABA analog.

2. A method of Claim 1 wherein the ratio of the GABA analog relative to the NK_1 receptor antagonist is from 50:1 to 1:1 expressed as parts by weight.

3. A method of Claim 1 wherein the ratio of the GABA analog relative to the NK_1 receptor antagonist is 20:1 expressed as parts by weight.

4. A method according to Claim 1 wherein the NK_1 receptor antagonist is [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)].

5. A method according to Claim 1 wherein the GABA analog is gabapentin.

6. A method according to Claim 1 wherein the GABA analog is pregabalin.

7. A method according to Claim 1 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and gabapentin.

8. A method according to Claim 1 employing [2-(1*H*-indol-3-yl)-1-methyl-1-(1-phenyl-ethylcarbamoyl)-ethyl]-carbamic acid benzofuran-2-ylmethyl ester [R-(R*,S*)] and pregabalin.

9. A method according to any one of claims 1 to 8 wherein the disorder treated is selected from anxiety, panic attacks, generalized anxiety disorder, social phobia or depression.

10. The use of a composition comprising synergistic amounts of a NK_1 receptor antagonist and a GABA analog effective in a psychiatric disorder, or pharmaceutically acceptable salts thereof, for the preparation of a medicament useful for preventing or treating a psychiatric disorder.

11. Use according to claim 10 characterized in that a psychiatric disorder is selected from anxiety, panic attacks, generalized anxiety disorder, social phobia and depression.

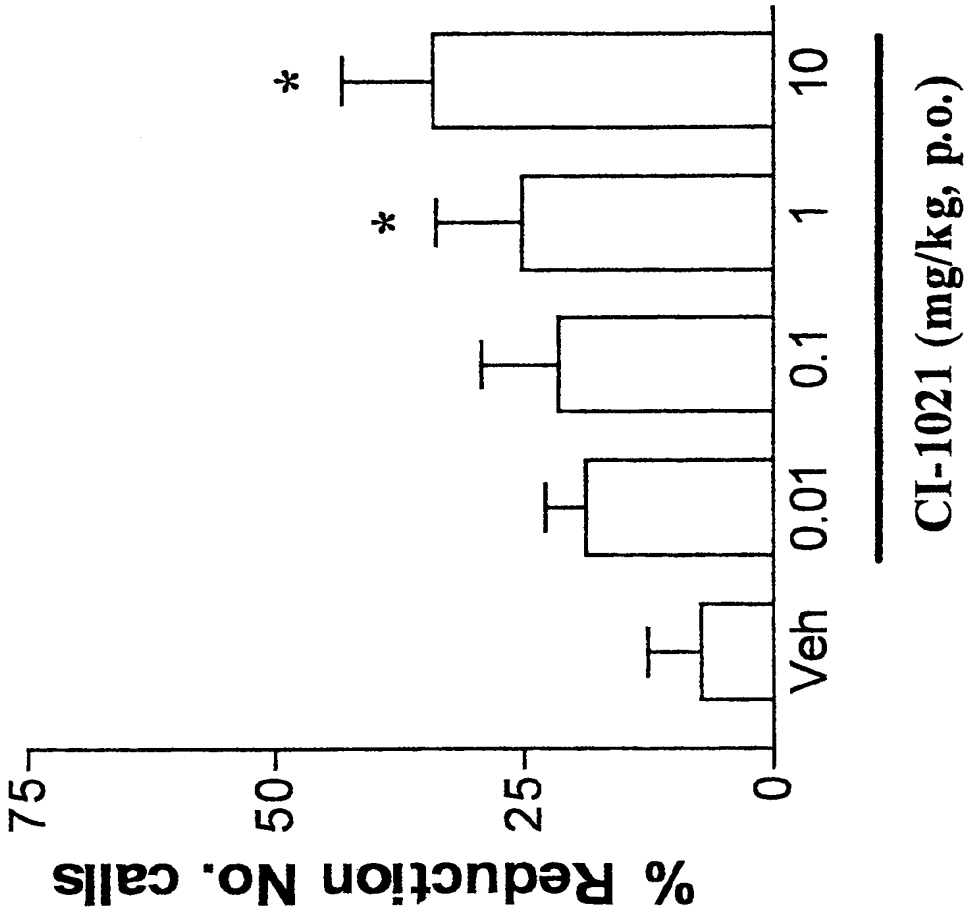


Figure 1:

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/EP 00/10084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/404 A61K31/40 A61P25/18 A61P25/24
A61K45/06 //(A61K31/40,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, MEDLINE, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98 24439 A (ELLIOTT JASON MATTHEW ;HOLLINGWORTH GREGORY JOHN (GB); KULAGOWSKI) 11 June 1998 (1998-06-11) page 3, line 20 - line 27 page 6, line 21 -page 7, line 31 Assay 4 ---	1-11
Y	WO 98 15277 A (CARLSON EMMA JOANNE ;MERCK SHARP & DOHME (GB); RUPNIAK NADIA MELAN) 16 April 1998 (1998-04-16) page 3, line 27 -page 4, line 6 page 5, line 30 -page 6, line 10 Assay 2 ---	1-11
Y	US 5 510 381 A (PANDE ATUL C) 23 April 1996 (1996-04-23) column 1, line 46 -column 2, line 54 --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2001	07/02/2001

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